DELETION OF INVENTORS

Please correct the inventorship under 37 CFR §1.48(b) by removing the following inventors from the present application:

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REMARKS

Applicants have amended the title and abstract to more specifically describe the invention. The specification has been amended to capitalize trademarks and remove reference to embedded hyperlinks.

Claim 1 has been amended to add the terms "isolated" and "specifically," and Claim 6 has been canceled. Applicants submit that no new matter has been added by these amendments, and that support for the amendments can be found throughout the specification. Support for the amendments can be found, for example, in the claims as originally filed, and at ¶ [0246] of the specification. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the canceled claim in this or any other patent application.

Claims 1-5 are presented for examination. For the reasons set forth below, Applicants respectfully traverse the rejections of the pending claims.

Priority Determination

The PTO has stated that the subject matter defined in the present application is not supported by the disclosure in any of the applications for which Applicants claim priority because the claimed subject matter does not have utility, enablement, or written description. The PTO therefore sets the priority under 35 U.S.C. §120 to the instant filing date, May 2, 2002.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. §120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. §120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. §120 to, PCT Application PCT/US00/14042 filed 5/22/2000, which is a continuation-in-part and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/099812 filed 9/10/1998.

Applicants submit that for the reasons stated below, the claimed antibodies have a credible, substantial, and specific utility. The sequence of SEQ ID NO: 52 was first disclosed in US Provisional Application 60/099812 filed 9/10/1998. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polypeptides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. For the reasons detailed below, Applicants submit they are entitled to at least the priority date of August 24, 2000.

Amendments to the Specification

Applicants have amended the title and abstract to be clearly indicative of the invention to which the claims are directed, as required by the Examiner.

Applicants have also amended the specification to recognize the trademark ATCC™ and other trademarks, and to remove browser-executable code.

Information Disclosure Statement

The Examiner requested that Applicants provide further information regarding the BLAST results included in the Information Disclosure Statement submitted Sept. 6, 2002. Applicants submit herewith another Supplemental Information Disclosure Statement providing the publication dates of the sequences identified in the BLAST search.

Claim Objections

The claims are objected to for improperly referencing the Figures. Applicants have amended the claims to remove reference to the Figures.

Correction of Inventorship under 37 CFR §1.48(b)

Applicant requests that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in §1.17(i) is submitted herewith.

Rejection Under 35 U.S.C. §101 – Utility

Claims 1-6 are rejected under 35 U.S.C. §101 as lacking patentable utility. The PTO states that the claimed invention is not supported by a specific, substantial and credible utility, or in the alternative, a well-established utility.

The PTO asserts that the claims are drawn to antibodies that bind the polypeptide shown in Figure 52 (SEQ ID NO:52), which is a totally new, uncharacterized polypeptide. The specification allegedly fails to disclose any secondary or tertiary structural features of the polypeptide, nor any biological activity, subcellular location, or physiological significance of the polypeptide. The PTO rejects the asserted utilities, stating that further research is necessary to establish a utility for the PRO1411 polypeptide and claimed antibodies.

The PTO acknowledges that the nucleic acid encoding PRO1411 was reported to be more highly expressed in normal skin tissue than in melanoma tumor tissue. However, the PTO states that the specification fails to disclose the number of samples tested, the statistical significance of the results, and the specific probe used for the analysis performed. The PTO believes that one skilled in the art "could not distinguish tumors from non-tumors based on the alleged 'more highly expressed' criteria only." Office Action at 7.

The PTO relies on Hu *et al.*, in support of its position that further research would be required to establish the statistical significance of the data provided, and whether and how a probe used in the PCR assay could be used as a diagnostic marker or therapeutic target. The PTO states that Hu *et al.* makes it clear that results such as those set forth in the present application are to be evaluated "very critically." Office Action at 8. The PTO also cites Haynes *et al.* for asserting that polypeptide levels cannot be accurately predicted from mRNA levels. The PTO states that "the lack of demonstrable correlation of mRNA expression levels with protein levels are so well known in the art at the time of filing, it was reported in a general text book" (Office Action at 9), and cites Genes VI, Chapter 29 (Benjamin Lewin, Genes VI (1997) as additional support. The PTO alleges that additional support is found in Gokman-Polar *et al.*, Anderson *et al.*, and Chen *et al.* The PTO concludes that given the totality of the evidence provided, "it is clear that those skilled in the art would not assume that an alleged increase in

gene copy number or increase in mRNA levels would correlate with increased polypeptide levels." Office Action at 10.

As discussed in more detail below, Applicants maintain that, as provided in Example 18 of the application, the polypeptide of SEQ ID NO: 52 is under-expressed in melanoma relative to normal skin and that this differential expression provides a specific, substantial and credible utility.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is

ready to be administered to humans." Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte*

examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic tools for cancer, particularly esophageal and kidney cancer. Applicants are not asserting that the claimed antibodies necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools, to assist in the diagnosis of certain cancers. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1411 polypeptide is expressed at least two-fold higher in normal skin compared to melanoma;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* a decrease, generally leads to a corresponding change in the level of the encoded protein, *e.g.* a decrease;

3. Given Applicants' evidence that the level of mRNA for the PRO1411 polypeptide is differentially expressed in melanoma as compared to normal skin tissue, it is more likely than not that the PRO1411 polypeptide is also differentially expressed in melanoma;

4. Antibodies to proteins which are differentially expressed in certain tumors are useful as diagnostic tools.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the reliability of the evidence reported in Example 18;

2. The PTO cites Hu *et al.*, Haynes *et al.*, Gokman-Polar *et al.*, Anderson *et al.*, Chen et al., and Lewin (Genes VI) to support the position that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, and that mRNA levels are not predictive of protein levels;

3. The PTO concludes that based on the cited literature, one of skill in the art would not assume that higher expression of mRNA would correlate with increased polypeptide levels. Therefore, further research needs to be done "to determine whether or not the polypeptide levels were higher, and whether the higher levels are statistically significant." Office Action at 10.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the Applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B (emphasis in original). First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18. Second, the Declaration of Chris Grimaldi, submitted herewith, further supports the data of Example 18. Third, Applicants submit that the cited references are not contrary to Applicants' arguments, and therefore are not evidence to support the PTO's position. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Applicants have established that the Gene Encoding the PRO1411 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1411 polypeptide in melanoma is insufficient because it does not disclose the number of samples tested, the statistical significance of the results, and the specific probe used for the analysis. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO1411 gene is differentially expressed in melanoma.

The gene expression data in the specification, Example 18, shows that the mRNA associated with protein PRO1411 was more highly expressed in normal skin tissue than in melanoma tissue. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal

human tissue samples. Identification of the differential expression of the PRO1411 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor. Applicants submit herewith as Exhibit 1 a copy of a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates

that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

The PTO cites Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) for support for its assertion the literature indicates that Applicants' results are to be evaluated very critically. The PTO states that Hu teaches that not all genes with increased expression in cancer have a known or published role in cancer.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role

for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker.

Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as molecular markers of cancer.

Applicants submit that a lack of known role for PRO1411 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1411 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

The position of the PTO is inconsistent with the analogous standard for therapeutic utility of a compound that "the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. §2701.01 (emphasis in original). Here, the mere

identification of altered expression in melanoma is relevant to the diagnosis of melanoma, and therefore provides an immediate benefit to the public.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1411 cDNA between melanoma and normal skin tissue. Therefore, it follows that expression levels of the PRO1411 gene can be used to distinguish melanoma from normal skin tissue. The PTO has not offered any significant arguments or evidence to the contrary.

As Applicants explain below, it is more likely than not that the PRO1411 polypeptide can also be used to distinguish melanoma from normal skin tissue. This provides utility for the claimed antibodies to the PRO1411 polypeptides.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1411 polypeptide in melanoma, it is more likely than not that the PRO1411 polypeptide is differentially expressed; and antibodies to proteins differentially expressed in certain tumors have utility as diagnostic tools.

In response to Applicants' assertion, the PTO cites Haynes *et al.*, Gokman-Polar *et al.*, Anderson *et al.*, Chen *et al.*, and Lewin as support for its argument that an increase in mRNA levels would not correlate with increased polypeptide levels. For the reasons discussed below, the cited references are not contrary to Applicants' asserted utility.

Haynes *et al.* studied whether there is a correlation between the level of mRNA expression and the level of protein expression for 80 selected genes from yeast. The genes were selected because they constituted a relatively homogeneous group with respect to predicted half-life and expression level of the protein products. *See* Haynes at 1863. Haynes did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Instead, Haynes determined whether the steady-state

transcript level correlated with the steady-state level of the corresponding protein based on an analysis of 80 different genes.

Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels (Fig. 1)." *Id.* However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, presented herein as Exhibit 2 (Gygi *et al.*, Molecular and Cellular Biology, Mar. 1999, 1720-1730). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi at 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. *Id.* Considering that Example18 of the specification shows over-expression of PRO 1344 mRNA in esophageal and kidney tumor, Haynes and Gygi actually provide strong evidence in support of a general correlation between mRNA and protein levels.

The PTO focuses on the portion of Haynes where the authors reported that for some of the studied genes with equivalent mRNA levels, there were differences in corresponding protein expression, including some that varied by more than 50-fold. Similarly, Haynes reports that different proteins with similar expression levels were maintained by transcript levels that varied by as much as 40-fold. *Id.* Thus, Haynes showed that for one type of yeast, similar mRNA levels for *different* genes did not universally result in equivalent protein levels for the *different* gene products, and similar protein levels for *different* gene products did not universally result from equivalent mRNA levels for the *different* genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, based on these results, Haynes concluded that protein levels cannot always be accurately predicted from the level of the corresponding mRNA transcript *when looking at the level of transcripts across different genes.*

Importantly, Haynes did <u>not</u> say that for a single gene, the level of mRNA transcript is not positively correlated with the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for the <u>same</u> gene leads to an increase or decrease for the corresponding protein. Haynes did <u>not</u> study this issue and says absolutely nothing about it.

As an analogy, consider a hypothetical study of the correlation between caloric intake and a person's weight. A researcher may find that twenty people with the same caloric intake have significantly different weights because they have significantly different life-styles (marathon runner versus sedentary). For the same reason, people with similar weights may have very different caloric intakes because of their lifestyles. One would conclude that caloric intake cannot be used to reliably predict a person's weight. However, if these same people increased their caloric intake, generally speaking, they would all begin to gain weight. Conversely, if they decreased their caloric intake this would generally lead to a decrease in their weights (assuming no major changes in lifestyle). Thus, the fact that one may not be able to accurately predict weight from caloric intake looking at a single data point across different people, does not mean that one cannot predict changes in weight from changes in caloric intake for a particular individual. This same principle applies to Applicants' assertion that there is a correlation between changes in mRNA level and changes in the level of the encoded protein. Because Haynes looks at a single data point across genes rather than at changes in the level of a single gene and protein, Haynes does not address Applicants' arguments. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO's position.

The PTO also cites Chen *et al.* for support for the assertion that polypeptide levels cannot be accurately predicted from mRNA levels. In Chen, the authors examined the relationship between mRNA levels and protein levels in 76 lung adenocarcinomas and 9 non-tumor lung samples. Like Haynes, Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across different genes. As discussed above with respect to Haynes, this measurement of a correlation across genes is not relevant to Applicants' asserted utility. Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins across the samples. Chen reports that 21.4% (21 of 98) of the genes showed a statistically significant correlation between protein and mRNA expression.

Chen provides scant evidence to counter Applicants' asserted utility for the claimed antibodies because portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between mRNA levels and corresponding protein levels

for mRNA that is differentially expressed in tumor cells relative to normal cells. Rather than looking for mRNAs which were differentially expressed, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level (Chen at 306, right column). Importantly, it is not known if there was any substantial difference in mRNA levels for the various genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed. Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value vs. protein value for three genes. In these figures, a wide range of mRNA expression levels were observed (approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' asserted correlation between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

The PTO relies on the fact that Chen also reports a lack of correlation for some mRNA/protein pairs to support its assertion that polypeptide levels cannot be accurately predicted from mRNA levels. However, the lack of correlation reported by Chen could be a result of a lack of substantial changes in mRNA level. This can be understood by again turning to Figures 2A-2C. As noted above, where a wide range of mRNA expression levels are seen, a correlation between mRNA and protein levels was observed. However, if one examines the data points within a small range of mRNA levels for these same genes, e.g. 500-600 or 5000-6000 in Figs. 2A-2C, it is clear that a correlation would not be detected for the data within this range. This does not mean that a correlation between changes in mRNA and protein does not exist for these genes, as is evident when larger changes in mRNA expression are included in the analysis. Instead, this indicates that for relatively small changes in mRNA, any correlation is masked by imprecision in the measurements.

Chen's experiment compared mRNA levels vs. protein levels across samples without selecting mRNA that showed a difference in expression level. And unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue. Since almost all samples tested by Chen were from the same type of tissue, few substantial variations in the level of mRNA or protein for a particular gene across the samples tested would be expected. Instead, it would be expected that most genes examined by Chen would have similar mRNA or protein levels across the samples. Figures 2A-2C of Chen demonstrate that the methods utilized by Chen cannot detect correlations between mRNA and protein levels when only small differences in mRNA expression are observed, but a correlation is detected when larger differences in mRNA expression are observed.

Accordingly, the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, confirms Applicants' assertion that substantial changes in mRNA levels (e.g., 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, this data also explains the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen. Thus, even given Chen's inability to detect a correlation between mRNA and protein in some genes, Chen's results do not refute Applicants' position.

Instead, Chen supports Applicants' position that a significant correlation between mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater. In further support of Applicants' position, Chen cites Celis *et al.* (FEBS Lett., 480:2-16 (2000)) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not relevant to Applicants' asserted utility, and therefore Chen's discussion of this issue and citation of Anderson and Seilhamer (Electrophoresis, 18:533-37 (1997)) and Gygi *et al.* (Mol. Cell. Bio., 19:1720-30 (1999)) offer no support for the PTO's position.

Even if the results in Chen supported the PTO's argument, which they do not as discussed above, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between changes in mRNA level and changes in protein level for an individual gene. There are other non-transcriptional mechanisms for

regulating gene and protein expression (*i.e.*, post-transcriptional regulation of genes, translation efficiency, etc.). However, as shown by the declarations, references, and textbooks discussed below, Applicants submit that the understanding in the art is that generally there is a correlation between a change in mRNA level and a change in protein level. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between **changes** in mRNA levels and **changes** in protein levels for a particular gene.

The Examiner also cites the textbook by Lewin as teaching that "... production of RNA cannot be inevitably be equated with production of protein" (page 487, column 2, last paragraph). Applicants note that the full statement from Lewin's textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) reads as follows: "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added). Further, Lewin goes on to state that transcription of a gene "is a major control point: probably **it is the most common level of regulation**." *Id.*, emphasis added. This reference provides additional support for Applicants' position that that the accepted understanding in the art is that there is a *reasonable* correlation between gene expression and the level of the encoded protein. Applicants do not assert that protein expression is never regulated at the translation level (*i.e.*, post-transcriptionally), but rather that, more often than not, regulation of protein expression occurs at the transcriptional level, making the level of mRNA a general indicator of the level of protein, and, more particularly, making changes in the level of mRNA a general indicator of changes in the level of protein. Far from rebutting this assertion, Lewin in fact supports it by stating that regulation occurs at the transcriptional stage in the overwhelming majority of cases, and that transcription is the most common level of regulation.

According to the Examiner, the lack of correlation between mRNA and protein levels is reconfirmed by a variety of studies such as that evidenced by Gokman-Polar *et al.* (Cancer Research 61:1375-1381, 2001) that indicates the absence of any necessary correlation between increased mRNA levels and increased protein levels. The PTO relies on a statement from

Gokman-Polar that "Quantitative reverse transcription-PCR analysis revealed that the PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isoenzyme expression is likely regulated at the posttranscriptional/translational level." Office Action at 9. However, a close review of the entire article indicates that with one exception, the data show that mRNA and protein levels are positively correlated, supporting Applicants assertion that increased mRNA levels correlate with increased protein levels. In Figure 2, the protein level of two isozymes shows a decrease, while the third is increased. This same pattern is seen for the corresponding mRNA levels in Figure 6, although admittedly the increase in mRNA for the third isozyme is minimal. Similarly, comparing the protein levels of the three isozymes in Figure 4 to the corresponding mRNA levels in Figure 7, with one exception the mRNA levels are positively correlated to protein levels. While protein levels do not increase or decrease in direct proportion to the changes in mRNA, five of the six examples show that protein levels are positively correlated to mRNA levels. This evidence is hardly sufficient to establish that one of skill in the art would reasonably doubt that there is a reasonable correlation between mRNA levels and protein levels.

The PTO also cites Anderson *et al.* (Electrophoresis, 18:533-37 (1997)) as teaching that "'Despite extensive work on the regulation of many individual genes, little attention appears to have been paid to the global question of the relation between mRNA and corresponding cellular protein abundances'" and that "the two major phages [sic] of gene expression regulation are of approximately equal importance in determining the net output of protein." Office Action at 9.

The teachings of Anderson are similar to those of Haynes. Anderson attempted to determine the overall level of correlation between mRNA and protein abundance for 19 genes in human liver. *Anderson* at Abstract. Protein abundance was measured as an average relative abundance in human liver samples. *Id.* at page 534, left column. Abundance of mRNA was measured from clones generated from human liver samples. *Id.* at page 534, right column. Anderson then plotted relative protein abundance for the 19 genes versus relative mRNA abundance. Anderson's plot contained 19 points, each point representing a different gene. *Id.* at page 535, Figure 1.

Anderson did not examine whether a **change** in transcript level for a particular gene led to a **change** in the level of expression of the corresponding protein. Anderson merely compared

the average mRNA/protein levels of different genes to explore a correlation between different genes. Anderson did not say that for a particular gene, the level of mRNA transcript does not correlate with the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for the same gene leads to an increase or decrease for the corresponding protein. Applicants' assertions could be illustrated by a two-dimensional plot showing various polypeptide concentrations of a particular gene as a function of various mRNA concentrations of that same gene. Anderson shows no such plot because it did not study this issue and says absolutely nothing about it. One cannot look at the level of mRNA across several different genes to investigate whether a change in the level of mRNA a particular gene leads to a change in the level of protein for that gene. Therefore, Anderson is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the Examiner's rejection of Applicants' asserted utility. As such, Anderson cannot support the Examiner's holding of a lack of utility for the claimed antibodies.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants submit herewith as Exhibit 3 a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith as Exhibit 4 a copy of the declaration of Paul Polakis, Ph.D., also an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in

> abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 5) and (4th ed. 2002) (submitted herewith as Exhibit 6)). Figure 9-2 of Exhibit 5 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 5 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 5 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 5 at 453 (emphasis added). Thus, as established in Exhibit 5, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 6, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 6 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 6 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 6 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for

regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 6 at 379 (emphasis added).

Additional support is found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 7. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 7 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 7 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 7 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 8, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Taken together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts from several leading textbooks and references provided above, all establish that the *generally accepted understanding in the art* is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Applicants submit that a lack of known role for PRO1411 in cancer does not prevent its use as a diagnostic tool for cancer. The fact that there is no known translocation or mutation of PRO1411, for example, is irrelevant to whether its differential expression can be used to assist in

diagnosis of cancer – one does not need to know why PRO1411 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies. (*See, e.g.,* U.S. Patent No. 6,414,117, U.S. Patent No. 6,124,433, U.S. Patent No. 6,156,500, and U.S. Patent No. 6,562,343 attached hereto as Exhibits 9-12.)

Accordingly, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1411 mRNA is more highly expressed in normal skin tissue than in melanoma tissue, the PRO1411 polypeptide will also be more highly expressed in normal skin tissue than in melanoma. This differential expression of the PRO1411 polypeptide makes antibodies to it useful as diagnostic tools for cancer.

Claimed antibodies would have diagnostic utility even if the protein were not over-expressed

Even assuming *arguendo* that there is no correlation between gene expression and increased protein expression for PRO1411, which Applicants submit is not true, an antibody to a polypeptide encoded by a gene that is differentially-expressed in cancer would still have a credible, specific and substantial utility. In support, Applicants submit herewith as Exhibit 13 the Declaration of Avi Ashkenazi, Ph.D., an expert in the field of cancer biology. Dr. Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate

> tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

This is echoed in paragraph 6 of the second Grimaldi Declaration. Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility, as would its antibodies. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed antibodies.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection is only sustained where the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**." M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by references and the declarations of skilled experts.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that antibodies to a polypeptide differentially expressed in certain tumors can be used as a diagnostic tool. None of the references cited by the Examiner support the PTO's position or is contrary to Applicants' asserted utility. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is credible and sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic tools for cancer, particularly melanoma.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies related to PRO1411. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1411 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene for the PRO1411 polypeptide is differentially expressed in melanoma as compared with normal skin tissue. These data are strong evidence that the PRO1411 gene and polypeptide are associated with skin cancer. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1411 gene and polypeptide with a specific disease. The asserted utility for antibodies to the PRO1411 polypeptide as diagnostic tools for cancer, particularly melanoma, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

The PTO has asserted the following arguments to support its conclusion that based on the cited literature, one of skill in the art would not assume that higher expression of mRNA would correlate with increased polypeptide levels: (1) the PTO has challenged the reliability of the evidence reported in Example 18; and (2) the PTO cites several references to support its assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, and that mRNA levels are not predictive of protein levels. The PTO states that further research needs to be done to determine whether the PRO1411 polypeptide is differentially expressed and whether the differential expression of the nucleic acid is statistically significant. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the gene expression data in Example 18 are real and significant. This declaration also indicates that given the relative difference of at least two-fold in expression levels, the disclosed nucleic acids and corresponding polypeptides and antibodies have utility as cancer diagnostic tools. Applicants have shown that Hu *et al.* does not support the PTO's position, and is not contrary to Applicants' asserted utility. Thus, the PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration.

Second, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in protein levels. Haynes *et al.* does not address this issue, and is not contrary to Applicants' asserted utility. Gokman-Polar *et al.*, Anderson *et al.*, Chen *et al.* and Lewin do not support the PTO's position and instead provide further support for Applicants' assertion that generally there is a correlation. Thus, the PTO has not offered any substantial reason or evidence to question these declarations and supporting references.

Third, Applicants have shown that it is not necessary to know what role PRO1411 plays in cancer to use it as a diagnostic tool. The PTO's own guidelines recognize this fact, and numerous patents have issued which claim differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because the PRO1411 gene and polypeptide are differentially expressed in melanoma cells compared to the corresponding normal skin cells. This is not a general utility that would apply to the broad class of antibodies.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies relating to PRO1411 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO also rejects Claims 1-6 under 35 U.S.C. §112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the rejection under 35 U.S.C. §101 above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Rejection 35 U.S.C. §112, second paragraph

The PTO has rejected Claims 1 and 6 as indefinite for the recitation of "an antibody that binds" and an "antibody that specifically binds". Claim 6 has been cancelled and Claim 1 amended to recite "specifically binds". Applicants submit that the term "specifically binds" has a well established meaning. Since claim terms should be given their ordinary, art-recognized meaning, the present rejection is believed to be overcome by the amendment.

Rejections Under 35 U.S.C. §102(b)

Claims 1-4 and 6 are rejected under 35. U.S.C. § 102(b) as anticipated by Valenzuela et al. (WO 99/55721, published 11-4-99). The Examiner also rejected Claims 1-6 35 U.S.C. §102(b) as anticipated by Ruben et al. (WO200061623, published 10-19-00).

As noted above, Applicants maintain that the present application is entitled to an earlier priority date. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed antibodies, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. As the November 4, 1999 publication date of Valenzuela et al. and the October 19, 2000 publication date of Ruben et al. are not more than one year before the August 24, 2000 filing date of the priority application, Applicants submit that the cited references are not prior art under 35 U.S.C. §102(b).

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §102(b).

Conclusion

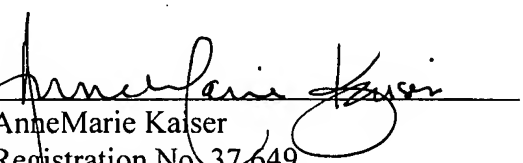
In view of the above, Applicants respectfully submit that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Nov. 17, 2005

By: 

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